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Abstract

Chronic use of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") has repeatedly been associated with deficits in working memory, declarative memory, and executive functions. However, previous findings regarding working memory and executive function are inconclusive yet, as in most studies concomitant stimulant use, which is known to affect these functions, was not adequately controlled for. Therefore, we compared the cognitive performance of 26 stimulant-free and largely pure (primary) MDMA users, 25 stimulant-using polydrug MDMA users, and 56 MDMA/stimulant-naïve controls by applying a comprehensive neuropsychological test battery. Neuropsychological tests were grouped into four cognitive domains. Recent drug use was objectively quantified by 6-month hair analyses on 17 substances and metabolites. Considerably lower mean hair concentrations of stimulants (amphetamine, methamphetamine, methylphenidate, cocaine), opioids (morphine, methadone, codeine), and hallucinogens (ketamine, 2C-B) were detected in primary compared to polydrug users, while both user groups did not differ in their MDMA hair concentration. Cohen's *d* effect sizes for both comparisons, i.e., primary MDMA users vs. controls and polydrug MDMA users vs. controls, were highest for declarative memory ($d_{primary}$=.90, $d_{polydrug}$=1.21), followed by working memory ($d_{primary}$=.52, $d_{polydrug}$=.96), executive functions ($d_{primary}$=.46, $d_{polydrug}$=.86), and attention ($d_{primary}$=.23, $d_{polydrug}$=.70). Thus, primary MDMA users showed strong and relatively discrete declarative memory impairments, whereas MDMA polydrug users displayed broad and unspecific cognitive impairments. Consequently, even largely pure chronic MDMA use is associated with decreased performance in declarative memory, while additional deficits in working memory and executive functions displayed by polydrug MDMA users are likely driven by stimulant co-use.

Keywords: cognition, entactogen, empathogen, MDEA, MDA, MDMA

1. Introduction

With an estimated 18.8 million past-year users, 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") remains one of the most used illicit drugs worldwide (United Nations Office on Drugs and Crime, 2016). MDMA is a synthetic substituted amphetamine derivate that blocks and reverses the monoamine transporters leading to a rapid release of monoamines, especially of serotonin (5-HT) but also of noradrenalin and dopamine (Kalant, 2001; Rudnick and Wall, 1992). In rodents and in non-human primates, research found evidence for long-term loss of 5-HT nerve terminals (Commins et al., 1987; Hatzidimitriou et al., 1999; Ricaurte et al., 1988). In humans, MDMA-related reductions of 5-HT transporters in different regions of the basal ganglia and the neocortex have been reported analogously (for review see Roberts et al., 2016b). Over the past three decades, the behavioral effects of MDMA use have been investigated extensively, and a broad range of cognitive dysfunctions has been reported in long-term MDMA users (Parrott, 2013).

While declarative memory impairments have been consistently shown in MDMA users with moderate to large effect sizes (for review see Kalechstein et al., 2007; Parrott, 2013), other cognitive domains yielded inconclusive results. The meta-analysis from Laws and Kokkalis (2007) found a medium effect size (d=0.63) for working memory (short-term memory) deficits in recreational MDMA users, but also reported that impairments are likely driven by verbal working memory deficits, whereas visual working memory may be primarily affected by cannabis use. On the other hand, working memory deficits found in the often applied (immediate) prose recall task (Morgan, 1999), which measures verbal working (immediate recall) and declarative memory (delayed recall), could not be replicated by all investigators (e.g., Thomasius et al., 2003; 2006). Moreover, a meta-regression over 12 comparisons revealed that differences in immediate prose recall between MDMA users (or ex-MDMA users) and controls are partially ascribable to the group's unequal intelligence status (Rogers et al., 2009). For delayed recall tasks (declarative memory), the same bias was found, but, in contrast to working memory performance, differences between MDMA users and controls remained significant after controlling for intelligence status (Rogers et al., 2009).

Regarding potential attention deficits in MDMA users, results seem to differ between studies investigating basic or higher order attention: Some studies examining basic attention or vigilance

reported no impairments (e.g., Back-Madruga et al., 2003; Parrott, 2013; Rodgers, 2000), in contrast to studies investigating higher order sustained attention that found strong impairments (Fox et al., 2001; McCann et al., 1999). However, in a meta-analytic review, Kalechstein (2007) reported only small to moderate effect sizes for attention/concentration deficits in MDMA users compared to matched controls. For executive functions, a recent meta-analysis by Roberts et al. (2016a) investigated four components of executive functions: inhibition, switching, updating (Miyake et al., 2000), and access (Fisk and Sharp, 2004) and found that – compared to non-MDMA polydrug using controls – polydrug MDMA users display significant alterations with a small effect size in all functions with exception of the unaffected inhibition component. However, the authors state that they cannot rule out the possibility that concomitant drug use contributed to the deficits found in executive functioning of the polydrug MDMA users.

Inconsistencies and interpretation difficulties within findings for cognitive deficits in long-term MDMA users – especially regarding working memory and attention - are apparent and may be partially explained by different factors limiting the interpretation of results. Perhaps the most serious disadvantages of human MDMA research are that drug consumption is mostly measured via self-reports (drug interviews) and that MDMA users often use other drugs (Schifano et al., 1998). Consequently, the interpretation of performance differences between MDMA users and controls in cross-sectional studies cannot be attributed solely to MDMA use (Curran, 2000). This is evident in experiments comparing polydrug MDMA users with drug-naïve controls, as possible long-term effects cannot be distinguished from the effects of other drugs. Also, in experiments with a non-MDMA polydrug control group, possible interaction effects between MDMA and other drugs may mask the pure effects of MDMA. Lastly, studies investigating non-polydrug MDMA users that do not quantitatively objectify (e.g., by toxicological hair testing) drug use remain unaware of the truth-value of the reported drug use patterns assessed with drug interviews. Because drug users might have different motivations to give a biased self-report or simply over- or underestimate their own consumption because of consistently shown memory alterations, we objectively quantified drug use through hair analyses in the present study.

To our knowledge, no study has investigated cognitive alterations in a sample of objectively confirmed pure MDMA users so far. Thus, we compared largely pure (in the following also called "primary" MDMA users) and polydrug MDMA users with drug-naïve healthy controls on well-established cognitive tasks. Drug use during the last months was objectively determined by quantitative hair analyses for all participants. We hypothesized that largely pure MDMA users still show disturbed declarative memory functions with a strong effect size, whereas other cognitive domains are only slightly or moderately impaired. In contrast, we expect stimulant-using polydrug MDMA users to show additional impairments in working memory, executive functions and attention given that these cognitive domains have been shown to be affected by cocaine (Jovanovski et al., 2005; Vonmoos et al., 2013; Vonmoos et al., 2014), amphetamine (Lundqvist, 2005), and methamphetamine use (Scott et al., 2007).

2. Experimental procedures

2.1 Participants

Within the context of the Zurich Cocaine Cognition Study ($ZuCo^2St$), which has started in 2010 (Quednow, 2016; Vonmoos et al., 2013), we recruited 53 long-term MDMA users and 56 drug-naïve, healthy controls by means of flyer and online media advertisements. Prior to testing, candidates underwent a brief telephone screening to assess their study eligibility. All subjects had to be aged between 18 and 60 years and had to have sufficient German language skills. Based on the results of the hair analyses (see below), 25 MDMA users were classified as polydrug MDMA users, 26 were classified as primary MDMA users and 2 MDMA users were excluded because of deficient/missing hair samples. Participants were categorized as primary MDMA users only if their hair analyses revealed MDMA consumption and the hair cocaine and amphetamine concentrations – the most common co-used drugs in our sample – did not exceed the cut-off values of 500pg/mg or 200pg/mg respectively (Cooper et al., 2012). Based on these cut-off values, we consequently classified participants as polydrug MDMA users if their amphetamine or cocaine hair concentrations exceeded these values and MDMA metabolites were detected (see Table 1 and Supplementary Table S1). This enabled us to compare 26 stimulant-free, primary MDMA users with 25 stimulant-using polydrug MDMA users, and 56 drug-naïve healthy controls. The groups were matched for age, sex, verbal intelligence, years of education, depression scores, and cannabis consumption during the past half year (Table 2).

The general exclusion criteria encompassed current or previous neurological disorders or head injuries, any clinically significant medical disease, a family history of schizophrenia or bipolar disorder, the prescription of drugs affecting the central nervous system, and a lifetime history of opioid use. Additionally, all participants who reported daily cannabis consumption were excluded. Controls were also excluded if they fulfilled the diagnostic criteria for any Axis-I *DSM-IV* psychiatric disorder including any form of addiction (except nicotine), or if they reported current or previous regular illegal drug use (except cannabis). Exclusion criteria for the MDMA groups were any acute or previous Axis-I *DSM-IV* adult psychiatric disorders with the exception of MDMA, alcohol, and nicotine misuse and a

history of depression (acute major depression was excluded). Inclusion criteria for the MDMA group were MDMA use of at least 100 occasions or weekly consumption during the last year, and a current abstinence period of less than 6 months.

All participants were asked to abstain from illegal substances for at least three days and from alcohol for at least 24h prior to testing. Drug urine screenings controlled for compliance (see below). The Cantonal Ethics Committee of Zurich has approved the study, and all participants gave written informed consent. The participants were compensated for their participation with 180 Swiss Francs.

2.2 Assessment measures

2.2.1 Clinical Assessment

Trained psychologists conducted the Structured Clinical Interview for Axis-I *DSM-IV* disorders in order to exclude participants with an Axis-I *DSM-IV* psychiatric disorder. Depressive symptoms were assessed with the Beck Depression Inventory (BDI) (Beck et al., 1961). Severity of ADHD symptoms was evaluated with the ADHD self-rating scale (ADHD-SR) corresponding to *DSM-IV* criteria (Rosler et al., 2004). Premorbid verbal intelligence was estimated with a German vocabulary test (*Mehrfachwahl-Wortschatz-Intelligenztest*) (Lehrl et al., 1995).

2.2.2 Drug use Assessment

Self-reported drug use was assessed with the Interview for Psychotropic Drug Consumption (Quednow et al., 2004). In addition, to objectively quantify the participant's drug use, hair samples were taken from the posterior vertex region of the head in order to determine the concentration of 17 common drugs and their metabolites by liquid chromatography-tandem mass spectroscopy (Cooper et al., 2012). To exclude intoxication at testing, urine drug screenings were employed by semi-quantitative enzyme multiplied immunoassay (see Supplementary Methods S1 for technical details).

2.2.3 Assessment of cognitive performance

Cognitive performance was assessed with four tests from the Cambridge Neuropsychological Test Automated Battery (Strauss et al., 2006): Rapid Visual Information Processing, Spatial Working Memory, Intra/Extra-Dimensional Set Shifting, and Paired Associates Learning. Furthermore, a German version of the Rey Auditory Verbal Learning Test (Helmstaedter et al., 2001) and the Letter Number Sequencing Task were administered (Wechsler, 1997). As previously published (Vonmoos et al., 2013; 2014), 15 predefined test parameters were z-transformed based on means and standard deviations of the control group and combined into four cognitive domains (Goldstein et al., 2004; Jovanovski et al., 2005; Pace-Schott et al., 2008; Vonmoos et al., 2013; Woicik et al., 2009): attention, working memory, declarative memory, and executive functions (see Supplementary Methods S3 for further details).

2.3 Statistical Analysis

We performed the statistical analyses with SPSS 22.0 for Windows. Demographic and drug use data for all groups were analyzed with Pearson's chi-square test and analyses of variance (ANOVA). To investigate group differences over all groups in cognitive parameters, we performed a multiple linear regression with the dummy coded (zero, 1) group variables as independent variables. To compare controls to the MDMA user groups, controls were chosen as the reference group, whereas for the comparison of the two MDMA using groups, polydrug MDMA users were coded 0 (Fig. 1 and Table 3). To be able to assess the practical significance of cognitive performance differences between controls and the MDMA using groups, Cohen's *d* effect sizes were calculated based on the means and pooled standard deviations (SD) of the two groups being compared (Cohen, 1988). Finally, we conducted multiple regression analyses (forced entry) to investigate the relationship between preselected predictors (age, sex, verbal IQ, grouping variables, BDI score and ADHD-SR score) and declarative memory performance. Further, multiple regression analyses were conducted over the MDMA users only to investigate possible factors influencing declarative memory performance in MDMA users; Model 1 estimated memory performance through drug use patterns covering the past six months (hair analyses and drug use per week) and in Model 2, estimations were based on drug use variables describing the duration of use or cumulative lifetime dose. Based on an à priori power

analysis with G*Power 3.1.9.2 (Faul et al., 2007) (Linear multiple regression: Fixed model, single regression coefficient, f^2=0.15, α= 0.05, two predictors), this study has an alpha-error probability of 5% and a power of over 85%.

3. Results

3.1 Demographic Characteristics and Drug Use

For demographic parameters, the groups did not differ significantly in age, verbal IQ, years of education, sex distribution, and depression scores (Table 2). For age, the middle 50% of all participants were aged between 22 and 29 years, while the youngest participant was 18 and the oldest 47 years old. However, both MDMA groups differed from controls with regard to their ADHD-SR scores. For objective drug-use measures, polydrug and primary MDMA users had significantly higher MDMA hair drug concentrations than controls but did not differ from each other. Importantly, only polydrug MDMA users differed from controls in amphetamine, cocaine and ketamine hair concentrations, whereas primary MDMA users only showed minimal exposure to these drugs (for detailed hair analyses of all MDMA users see Table 1). For cannabis, amphetamine, and cocaine, primary MDMA users showed no significant differences regarding positive urine tests compared to controls, while the polydrug MDMA user group contained three cocaine-positive urine analyses. Primary MDMA users did not differ significantly from controls in any tobacco, alcohol, and cannabis measure, while polydrug MDMA users reported stronger current smoking and drinking habits.

3.2 Cognition

Significant regression equations with the dummy coded group variables were found for all four z-transformed domains of attention ($F(2,104)=4.591$, $p<.05$), working memory ($F(2,104)=9.584$, $p<.001$), declarative memory ($F(2,104)=21.187$, $p<.001$), and executive functions ($F(2,104)=7.297$, $p<.01$). Group differences between controls and polydrug MDMA users were significant for all four domains ($p<.01$-$.001$), whereas group differences between controls and primary MDMA users only reached significance for working memory ($p<.05$) and declarative memory ($p<.01$) performance (Table 3). Effect sizes for performance differences over the four domains are shown in Figure 1. For polydrug MDMA vs. controls, working memory, declarative memory and executive functions reached large effect sizes (d=0.96, 1.21, and 0.86 respectively), while attention difficulties reached a moderate to large effect size (d=0.70). For the comparison of primary MDMA users and controls, only

declarative memory impairments reached a large effect size (d=0.90), whereas working memory as well as executive functions displayed moderate and attention only small effect sizes. Accordingly, for the single cognitive parameters depicted in Figure 2, only comparisons between polydrug MDMA users and controls reached large effect sizes of 0.8 and higher. For primary MDMA users vs. controls, the largest effect sizes were found for verbal (RAVLT) and visuo-spatial (PAL) declarative memory measures.

3.3 Regression models

To analyze potential cofactors and dose-response effects on declarative memory performance multiple regression analyses were performed. These analyses over all participants (n=106) for demographic variables (age, sex, and verbal IQ) and group contrasts revealed that being either a primary or a polydrug MDMA user significantly decreases the intercept of the regression equation of declarative memory performance (β=-.232, t=-2.76, p<.01, and β=-.508, t=-5.97, p<.001). As expected, the significant coefficients for age and verbal IQ were negative and positive respectively. The regression model was significant (R^2=0.37, $F_{5,\ 105}$=11.753, p<.001). The model only explained 2.1% more variance after adding the BDI and the ADHD-SR sum score in a second step (p=.183) (Supplementary Table S2). Neither of the two variables predicted declarative memory performance significantly (p=.101 and p=.130).

The association between declarative memory performance and drug use parameters was assessed with two models covering either the past six month (Model 1) or lifetime substance use (Model 2) of the MDMA users (n=51). Model 1 contained the following variables: cannabis consumption in grams per week, the amount of cigarettes smoked per day, amount of alcohol consumed per week, MDMA hair concentration, and a grouping variable that differentiated between primary and polydrug MDMA users to account for stimulant use (Supplementary Table S3). None of the drug parameters predicted declarative memory performance. However, the grouping variable showed that polydrug substance use decreased the intercept (t=-1.93, p=.059, β=-.279).

Model 2, which contained drug use parameters concerning lifetime drug consumption, revealed that – within MDMA users – lifetime cannabis consumption predicted declarative memory performance

(p<.05) when duration of alcohol and nicotine use and lifetime MDMA consumption were held constant (Supplementary Table S4).

4. Discussion

The aim of the study was to investigate the cognitive performance of objectively verified, primary and largely pure MDMA users. Detailed psychiatric diagnostics, hair toxicology, and an exact matching procedure minimized the influence of psychiatric comorbidities and underreported drug use. We demonstrated that primary and polydrug long-term MDMA users show medium to strong cognitive impairments in declarative memory and that, in contrast to polydrug MDMA users, primary MDMA users show only small and moderate impairments in the domains of attention, working memory, and executive functions compared with drug-naïve controls. The data of this study confirm previously shown memory deficits in abstinent long-term MDMA users and thus deliver evidence for declarative memory impairments even in largely pure recreational MDMA users with no or minimal stimulant co-use.

In line with previous meta-analyses (Kalechstein et al., 2007; Laws and Kokkalis, 2007; Rogers et al., 2009), our data show that the strongest impairments have to be expected in declarative memory functions after repeated MDMA consumption, which confirms our hypothesis. Task-specifically, decreased delayed verbal memory performance (RAVLT) can be considered the "main symptom" of MDMA misuse as the variable *delayed recall* has been repeatedly shown to differentiate between MDMA users and controls (Fox et al., 2001; Quednow et al., 2006; Reneman et al., 2000) and revealed the strongest effect size in this study for polydrug MDMA users as well as for primary MDMA users. In line with previous findings (Laws and Kokkalis, 2007), effect sizes for verbal memory deficits were larger than for visual memory deficits in MDMA users. Regarding the PAL measures, our data are in accordance with previous studies showing that polydrug MDMA users required more trials to complete the task compared to polydrug controls (Fox et al., 2002). Taken together, the individual variables of our declarative memory domain indicate moderate to large impairments (d=0.62-1.1) in visual, spatial and verbal learning and recognition processes.

Regarding working memory deficits, the primary MDMA users performed worse than controls on the domain level only with a medium effect size (d=0.52), whereas polydrug MDMA users showed strong working memory impairments (d=0.96). This discrepancy in performance may explain the

inconsistencies in previous findings and underline the additional detrimental effect of stimulant use on working memory (Vonmoos et al., 2013; 2014). Interestingly, primary MDMA users did not differ substantially from controls in two out of three measures for working memory, *LNST score* and *total errors in the SWM task*. Both measures are widely accepted measures for working memory performance (Crowe, 2000; Morris et al., 1988) and have previously been linked to MDMA-induced deficits (Fox et al., 2002; 2005). Our data do not replicate these findings for largely pure MDMA users but support our hypothesis that working memory deficits in polydrug MDMA users are likely stimulant-driven, and consequently, that past findings may be explained by undetected stimulant co-consumption. It is noteworthy that – although our working memory domain differentiated significantly between controls and primary MDMA users – only the underlying *first trial memory score* (PAL) reached significance. This variable was viewed as a measure for passive storage ability and has shown to correlate stronger with verbal than with non-verbal memory parameters, probably because subjects verbalize the patterns and/or places which have to be remembered (Torgersen et al., 2012). In the context of Fox et al.'s (2001) suggestion that verbal learning problems in MDMA users are associated with storage and retrieval problems, and the finding that MDMA use affects verbal memory more strongly than visual memory, it can be argued that working memory performance between primary MDMA users and controls might in sum be less impaired then our working memory domain suggests at a first glance. Alternatively, the moderate working memory impairment displayed by our primary MDMA user group might be a result of past stimulant consumption, which may have occurred before the time span captured by the hair analyses. This idea is supported by a significant negative correlation between working memory performance and self-reported lifetime cocaine consumption across all MDMA users ($r(49)=-.40$, $p<.01$).

For primary MDMA users, we did not find any significant results in the domains of executive functions and attention except for the RAVLT parameter *recall consistency*, which contrasts with previous studies that found executive function and decision-making impairments in MDMA users (Fisk and Montgomery, 2009; Fisk et al., 2004; Montgomery et al., 2005; Quednow et al., 2007; Roberts et al., 2016a). On the other hand, Montgomery et al. (2005) – who investigated the executive functions specifically – found no impairments in MDMA users compared to controls in switching,

which is – besides updating – tested by the Intra-Extra Dimensional Set Shift Task (IED) applied in the present study. In line with Montgomery et al. (2005) we did not find changes in the IED performance in primary MDMA users. Interestingly, the only variable assessing executive functions that reached significance (*recall consistency*, RAVLT) strongly involves verbal memory in contrast to the other, non-significant variables involving visual memory processes. As mentioned before, results vary regarding attentional performance of MDMA users, which is also reflected in our results; in all three parameters measuring attention, the polydrug MDMA users performed significantly worse than controls with moderate effect sizes, whereas primary MDMA users did not differ substantially from controls. These results are in line with previous research as 1) stimulant users were shown to perform worse than drug-naïve controls in an equally created attention domain (Vonmoos et al., 2013), and 2) as basic attentional and executive functions are generally unaffected in MDMA users compared to polydrug or cannabis using control groups (Medina et al., 2005; Parrott, 2001; Rogers et al., 2009). Interestingly, in contrast to our polydrug MDMA users, largely pure cocaine users did not differ from stimulant-naïve controls in the RAVLT *supraspan* in a previous study from our lab (Vonmoos et al., 2013). Future research should therefore investigate possible interaction effects of MDMA and stimulant consumption more in depth, especially because animal studies revealed that the simultaneous administration of MDMA (or MDMA analogues) and a prodopaminergic agent leads to a potentiation of the serotonin neurotoxicity of MDMA (Clemens et al., 2005; Johnson et al., 1991; Johnson and Nichols, 1991; Schmidt et al., 1991).

The results of our regression analysis for demographic variables support the notion of declarative memory deficits in abstinent primary MDMA users, as group contrasts remained significant even when sex, age, and verbal IQ were held constant. By adding the BDI and ADHD-SR sum core, the model only improved marginally. We have previously investigated the effects of depression and ADHD symptoms on cognitive performance in cocaine users and found that both factors, ADHD and depression scores, were associated with worse cognitive performance in cocaine users (Vonmoos et al., 2013; Wunderli et al., 2016). We therefore expected to find significant contributions of these two variables in the regression model again. However, probably due to the relative small variance in BDI

and ADHS-SR scores and the matching process (exclusion of psychiatric disorders), declarative memory was not significantly predicted through these two measures.

Model 1, which predicted declarative memory performance through drug use parameters covering the past six months, revealed no significant associations except for the grouping variable that distinguished between primary and polydrug MDMA users. Although this grouping variable only predicted declarative memory performance by trend ($p=.059$), the importance of stimulant co-consumption is emphasized by the fact that polydrug MDMA users displayed higher – although none significantly higher – mean values in all of the other predictors.

In Model 2, declarative memory performance was aimed to be predicted by factors covering cumulative lifetime drug use estimates. Although the whole model predicted declarative memory performance by trend only, it revealed that the estimated lifetime dose of cannabis was negatively associated with memory performance. Additionally, the grouping variable still predicted memory performance with constant drug factors by trend. It was postulated previously that cognitive deficits in MDMA users can be explained by cannabis co-use alone (Croft et al., 2001). Our data do not support this assumption because the two user groups still differ in declarative memory performance when the effect of cannabis consumption is held constant. This finding is therefore in line with previous studies demonstrating memory deficits in MDMA users, even when concomitant cannabis use was introduced as a covariate or when MDMA users were compared to cannabis using controls (Fox et al., 2001; Quednow et al., 2006). However, our results support the notion that cannabis is an important confound when cognitive performance is measured in MDMA users (Croft et al., 2001; Simon and Mattick, 2002), although the cannabis use intensity was relatively low in our sample.

Finally, in both models, severity of MDMA consumption did not predict declarative memory performance (MDMA hair concentration and lifetime dose). Previous literature is inconclusive about the correlation between MDMA dose and strength of impairments. Many researchers reported dose-related impairments in MDMA users (Bolla et al., 1998; Gouzoulis-Mayfrank et al., 2000; Montgomery et al., 2005; Quednow et al., 2006). These findings were usually interpreted as evidence for selective, neurotoxic effects on the 5-HT system (Gouzoulis-Mayfrank et al., 2003; Parrott, 2002; Quednow et al., 2006; Quednow et al., 2004). On the other hand, Laws and Kokkalis (2007) found no

continuous relationship of lifetime MDMA consumption of MDMA and memory measures in their meta-analysis and therefore proposed a rather stepwise relationship between MDMA use and memory decline. This explanation is in line with a recent, longitudinal study that only found marginally significant changes in recall measures in stimulant-using polydrug MDMA users over a 2 year period (Wagner et al., 2015). Because neither MDMA hair concentrations nor self-reported amount of lifetime MDMA consumption significantly predicted memory performance, our data support this model of a stepwise relationship between MDMA use and memory decline. Moreover, also duration of abstinence did not predict memory performance in our sample (β=.010, t=0.70, p=.945). An alternative explanation of these discrepancies may lie in the variability of the purity of MDMA tablets potentially leading to different results across studies (Morgan, 1999; Parrott, 2004). In fact, recent analyses in the context of the Swiss Drug Checking program showed that only 7.1% of the ecstasy samples (n=210) tested in 2016 contained psychoactive substances other than MDMA (see http://www.saferparty.ch/125.html).

This study has some limitations. First, human MDMA research practice was criticized for applying unreliable self-reported drug assessments (Cole, 2014). Although we objectively quantified participants drug use via hair analyses, we had to rely on participants self-reports for alcohol, nicotine, and cannabis consumption. Obviously, in a sample in which memory deficits can be expected, self-reported drug assessment might be less reliable. Nonetheless, we aimed to minimize the influence of these drugs by matching the groups accordingly. Second, there is the possibility that cognitive differences are based on pre-existing differences and that predispositions are responsible for drug use and cognitive impairments. This limitation can be controlled by adding a polydrug control group. However, the present investigation is a cross-sectional study that is not suitable to differentiate between predisposing factors and drug-induced alterations.

Taken together, our data suggest that the combined use of MDMA and stimulants is associated with a strongly increased risk for cognitive impairments compared to primary MDMA consumption and that the pronounced working memory and executive function impairments in polydrug MDMA users are likely driven by stimulant co-use. However, primary MDMA users showed robust and strong

alterations of declarative long-term memory. The considerable performance difference of primary vs. polydrug MDMA users together with the finding that cannabis additionally impairs memory performance in MDMA users highlights the need for objective group assessments in human MDMA research. Future research should therefore distinguish between stimulant using and primary MDMA users while the influence of other drugs of abuse but especially cannabis consumption should be either excluded or controlled for by matching or an additional cannabis-only user group.

References

Back-Madruga, C., Boone, K.B., Chang, L., Grob, C.S., Lee, A., Nations, H., Poland, R.E., 2003. Neuropsychological effects of 3,4-methylenedioxymethamphetamine (MDMA or ecstasy) in recreational users. Clin Neuropsychol 17, 446-459.

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. Archives of general psychiatry 4, 561-571.

Bolla, K.I., McCann, U.D., Ricaurte, G.A., 1998. Memory impairment in abstinent MDMA ("Ecstasy") users. Neurology 51, 1532-1537.

Clemens, K.J., Cornish, J.L., Li, K.M., Hunt, G.E., McGregor, I.S., 2005. MDMA ('Ecstasy') and methamphetamine combined: order of administration influences hyperthermic and long-term adverse effects in female rats. Neuropharmacology 49, 195-207.

Cohen, J., 1988. Statistical power analysis for the behavioral sciences, 2 ed. Lawrence Erlbaum Associates, Hillsdale, NJ.

Cole, J.C., 2014. MDMA and the "ecstasy paradigm". J Psychoactive Drugs 46, 44-56.

Commins, D.L., Vosmer, G., Virus, R.M., Woolverton, W.L., Schuster, C.R., Seiden, L.S., 1987. Biochemical and histological evidence that methylenedioxymethylamphetamine (MDMA) is toxic to neurons in the rat brain. J Pharmacol Exp Ther 241, 338-345.

Cooper, G.A., Kronstrand, R., Kintz, P., Society of Hair, T., 2012. Society of Hair Testing guidelines for drug testing in hair. Forensic Sci Int 218, 20-24.

Croft, R.J., Mackay, A.J., Mills, A.T., Gruzelier, J.G., 2001. The relative contributions of ecstasy and cannabis to cognitive impairment. Psychopharmacology (Berl) 153, 373-379.

Crowe, S.F., 2000. Does the letter number sequencing task measure anything more than digit span? Assessment 7, 113-117.

Curran, H.V., 2000. Is MDMA ('Ecstasy') neurotoxic in humans? An overview of evidence and of methodological problems in research. Neuropsychobiology 42, 34-41.

Faul, F., Erdfelder, E., Lang, A.G., Buchner, A., 2007. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 39, 175-191.

Fisk, J.E., Montgomery, C., 2009. Evidence for selective executive function deficits in ecstasy/polydrug users. J Psychopharmacol 23, 40-50.

Fisk, J.E., Montgomery, C., Murphy, P., Wareing, M., 2004. Evidence for executive deficits among users of MDMA (Ecstasy). Br J Psychol 95, 457-466.

Fisk, J.E., Sharp, C.A., 2004. Age-related impairment in executive functioning: updating, inhibition, shifting, and access. Journal of clinical and experimental neuropsychology 26, 874-890.

Fox, H.C., McLean, A., Turner, J.J., Parrott, A.C., Rogers, R., Sahakian, B.J., 2002. Neuropsychological evidence of a relatively selective profile of temporal dysfunction in drug-free MDMA ("ecstasy") polydrug users. Psychopharmacology (Berl) 162, 203-214.

Fox, H.C., Toplis, A.S., Turner, J.J., Parrott, A.C., 2001. Auditory verbal learning in drug-free Ecstasy polydrug users. Hum Psychopharmacol 16, 613-618.

Goldstein, R.Z., Leskovjan, A.C., Hoff, A.L., Hitzemann, R., Bashan, F., Khalsa, S.S., Wang, G.J., Fowler, J.S., Volkow, N.D., 2004. Severity of neuropsychological impairment in cocaine and alcohol addiction: association with metabolism in the prefrontal cortex. Neuropsychologia 42, 1447-1458.

Gouzoulis-Mayfrank, E., Daumann, J., Tuchtenhagen, F., Pelz, S., Becker, S., Kunert, H.J., Fimm, B., Sass, H., 2000. Impaired cognitive performance in drug free users of recreational ecstasy (MDMA). J Neurol Neurosurg Psychiatry 68, 719-725.

Gouzoulis-Mayfrank, E., Thimm, B., Rezk, M., Hensen, G., Daumann, J., 2003. Memory impairment suggests hippocampal dysfunction in abstinent ecstasy users. Prog Neuropsychopharmacol Biol Psychiatry 27, 819-827.

Hatzidimitriou, G., McCann, U.D., Ricaurte, G.A., 1999. Altered serotonin innervation patterns in the forebrain of monkeys treated with (+/-)3,4-methylenedioxymethamphetamine seven years previously: factors influencing abnormal recovery. J Neurosci 19, 5096-5107.

Helmstaedter, C., Lendt, M., Lux, S., 2001. Verbaler Lern- und Merkfähigkeitstest. Beltz, Göttingen.

Johnson, M.P., Huang, X.M., Nichols, D.E., 1991. Serotonin neurotoxicity in rats after combined treatment with a dopaminergic agent followed by a nonneurotoxic 3,4-methylenedioxymethamphetamine (MDMA) analogue. Pharmacol Biochem Behav 40, 915-922.

Johnson, M.P., Nichols, D.E., 1991. Combined administration of a non-neurotoxic 3,4-methylenedioxymethamphetamine analogue with amphetamine produces serotonin neurotoxicity in rats. Neuropharmacology 30, 819-822.

Jovanovski, D., Erb, S., Zakzanis, K.K., 2005. Neurocognitive deficits in cocaine users: a quantitative review of the evidence. Journal of clinical and experimental neuropsychology 27, 189-204.

Kalant, H., 2001. The pharmacology and toxicology of "ecstasy" (MDMA) and related drugs. CMAJ 165, 917-928.

Kalechstein, A.D., De La Garza, R., 2nd, Mahoney, J.J., 3rd, Fantegrossi, W.E., Newton, T.F., 2007. MDMA use and neurocognition: a meta-analytic review. Psychopharmacology (Berl) 189, 531-537.

Laws, K.R., Kokkalis, J., 2007. Ecstasy (MDMA) and memory function: a meta-analytic update. Hum Psychopharmacol 22, 381-388.

Lehrl, S., Triebig, G., Fischer, B., 1995. Multiple choice vocabulary test MWT as a valid and short test to estimate premorbid intelligence. Acta neurologica Scandinavica 91, 335-345.

Lundqvist, T., 2005. Cognitive consequences of cannabis use: comparison with abuse of stimulants and heroin with regard to attention, memory and executive functions. Pharmacol Biochem Behav 81, 319-330.

McCann, U.D., Mertl, M., Eligulashvili, V., Ricaurte, G.A., 1999. Cognitive performance in (+/-) 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") users: a controlled study. Psychopharmacology (Berl) 143, 417-425.

Medina, K.L., Shear, P.K., Corcoran, K., 2005. Ecstasy (MDMA) exposure and neuropsychological functioning: a polydrug perspective. J Int Neuropsychol Soc 11, 753-765.

Miyake, A., Friedman, N.P., Emerson, M.J., Witzki, A.H., Howerter, A., Wager, T.D., 2000. The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. Cogn Psychol 41, 49-100.

Montgomery, C., Fisk, J.E., Newcombe, R., Murphy, P.N., 2005. The differential effects of ecstasy/polydrug use on executive components: shifting, inhibition, updating and access to semantic memory. Psychopharmacology (Berl) 182, 262-276.

Morgan, M.J., 1999. Memory deficits associated with recreational use of "ecstasy" (MDMA). Psychopharmacology (Berl) 141, 30-36.

Morris, R.G., Downes, J.J., Sahakian, B.J., Evenden, J.L., Heald, A., Robbins, T.W., 1988. Planning and spatial working memory in Parkinson's disease. J Neurol Neurosurg Psychiatry 51, 757-766.

Pace-Schott, E.F., Morgan, P.T., Malison, R.T., Hart, C.L., Edgar, C., Walker, M., Stickgold, R., 2008. Cocaine users differ from normals on cognitive tasks which show poorer performance during drug abstinence. The American journal of drug and alcohol abuse 34, 109-121.

Parrott, A.C., 2001. Human psychopharmacology of Ecstasy (MDMA): a review of 15 years of empirical research. Hum Psychopharmacol 16, 557-577.

Parrott, A.C., 2002. Recreational Ecstasy/MDMA, the serotonin syndrome, and serotonergic neurotoxicity. Pharmacol Biochem Behav 71, 837-844.

Parrott, A.C., 2004. Is ecstasy MDMA? A review of the proportion of ecstasy tablets containing MDMA, their dosage levels, and the changing perceptions of purity. Psychopharmacology (Berl) 173, 234-241.

Parrott, A.C., 2013. Human psychobiology of MDMA or 'Ecstasy': an overview of 25 years of empirical research. Hum Psychopharmacol 28, 289-307.

Quednow, B.B., 2016. The rise of the ego: social cognition and interaction in cocaine users., in: Preedy, V.R. (Ed.), Neuropathology of Drug Addictions and Substance Misuse, 1st Edition ed. Academic Press, London, pp. 257-268.

Quednow, B.B., Jessen, F., Kuhn, K.U., Maier, W., Daum, I., Wagner, M., 2006. Memory deficits in abstinent MDMA (ecstasy) users: neuropsychological evidence of frontal dysfunction. J Psychopharmacol 20, 373-384.

Quednow, B.B., Kuhn, K.U., Hoenig, K., Maier, W., Wagner, M., 2004. Prepulse inhibition and habituation of acoustic startle response in male MDMA ('ecstasy') users, cannabis users, and healthy controls. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 29, 982-990.

Quednow, B.B., Kuhn, K.U., Hoppe, C., Westheide, J., Maier, W., Daum, I., Wagner, M., 2007. Elevated impulsivity and impaired decision-making cognition in heavy users of MDMA ("Ecstasy"). Psychopharmacology (Berl) 189, 517-530.

Reneman, L., Booij, J., Schmand, B., van den Brink, W., Gunning, B., 2000. Memory disturbances in "Ecstasy" users are correlated with an altered brain serotonin neurotransmission. Psychopharmacology (Berl) 148, 322-324.

Ricaurte, G.A., DeLanney, L.E., Irwin, I., Langston, J.W., 1988. Toxic effects of MDMA on central serotonergic neurons in the primate: importance of route and frequency of drug administration. Brain Res 446, 165-168.

Roberts, C.A., Jones, A., Montgomery, C., 2016a. Meta-analysis of executive functioning in ecstasy/polydrug users. Psychol Med 46, 1581-1596.

Roberts, C.A., Jones, A., Montgomery, C., 2016b. Meta-analysis of molecular imaging of serotonin transporters in ecstasy/polydrug users. Neuroscience and biobehavioral reviews 63, 158-167.

Rodgers, J., 2000. Cognitive performance amongst recreational users of "ecstasy". Psychopharmacology (Berl) 151, 19-24.

Rogers, G., Elston, J., Garside, R., Roome, C., Taylor, R., Younger, P., Zawada, A., Somerville, M., 2009. The harmful health effects of recreational ecstasy: a systematic review of observational evidence. Health Technol Assess 13, iii-iv, ix-xii, 1-315.

Rosler, M., Retz, W., Retz-Junginger, P., Thome, J., Supprian, T., Nissen, T., Stieglitz, R.D., Blocher, D., Hengesch, G., Trott, G.E., 2004. Tools for the diagnosis of attention-deficit/hyperactivity disorder in adults. Self-rating behaviour questionnaire and diagnostic checklist. Der Nervenarzt 75, 888-895.

Rudnick, G., Wall, S.C., 1992. The molecular mechanism of "ecstasy" [3,4-methylenedioxy-methamphetamine (MDMA)]: serotonin transporters are targets for MDMA-induced serotonin release. Proc Natl Acad Sci U S A 89, 1817-1821.

Schifano, F., Di Furia, L., Forza, G., Minicuci, N., Bricolo, R., 1998. MDMA ('ecstasy') consumption in the context of polydrug abuse: a report on 150 patients. Drug Alcohol Depend 52, 85-90.

Schmidt, C.J., Black, C.K., Taylor, V.L., 1991. L-DOPA potentiation of the serotonergic deficits due to a single administration of 3,4-methylenedioxymethamphetamine, p-chloroamphetamine or methamphetamine to rats. Eur J Pharmacol 203, 41-49.

Scott, J.C., Woods, S.P., Matt, G.E., Meyer, R.A., Heaton, R.K., Atkinson, J.H., Grant, I., 2007. Neurocognitive effects of methamphetamine: a critical review and meta-analysis. Neuropsychology review 17, 275-297.

Simon, N.G., Mattick, R.P., 2002. The impact of regular ecstasy use on memory function. Addiction 97, 1523-1529.

Strauss, E., Sherman, E.M., Spreen, O., 2006. A compendium of neuropsychological tests: Administration, norms, and commentary. Oxford University Press.

Thomasius, R., Petersen, K., Buchert, R., Andresen, B., Zapletalova, P., Wartberg, L., Nebeling, B., Schmoldt, A., 2003. Mood, cognition and serotonin transporter availability in current and former ecstasy (MDMA) users. Psychopharmacology (Berl) 167, 85-96.

Thomasius, R., Zapletalova, P., Petersen, K., Buchert, R., Andresen, B., Wartberg, L., Nebeling, B., Schmoldt, A., 2006. Mood, cognition and serotonin transporter availability in current and former ecstasy (MDMA) users: the longitudinal perspective. J Psychopharmacol 20, 211-225.

Torgersen, J., Flaatten, H., Engelsen, B., Gramstad, A., 2012. Cinical validation of Cambridge Neuropsychological Test Automated Battery in a Norwegian Epilepsy Population. Journal of Behavioral and Brain Science 2, 108-116.

United Nations Office on Drugs and Crime, 2016. World Drug Report 2016. United Nations Publication, Vienna.

Verdejo-Garcia, A.J., Lopez-Torrecillas, F., Aguilar de Arcos, F., Perez-Garcia, M., 2005. Differential effects of MDMA, cocaine, and cannabis use severity on distinctive components of the executive functions in polysubstance users: a multiple regression analysis. Addict Behav 30, 89-101.

Vonmoos, M., Hulka, L.M., Preller, K.H., Jenni, D., Baumgartner, M.R., Stohler, R., Bolla, K.I., Quednow, B.B., 2013. Cognitive dysfunctions in recreational and dependent cocaine users: role

of attention-deficit hyperactivity disorder, craving and early age at onset. The British journal of psychiatry : the journal of mental science 203, 35-43.

Vonmoos, M., Hulka, L.M., Preller, K.H., Minder, F., Baumgartner, M.R., Quednow, B.B., 2014. Cognitive impairment in cocaine users is drug-induced but partially reversible: evidence from a longitudinal study. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 39, 2200-2210.

Wagner, D., Tkotz, S., Koester, P., Becker, B., Gouzoulis-Mayfrank, E., Daumann, J., 2015. Learning, Memory, and Executive Function in New MDMA Users: A 2-Year Follow-Up Study. Front Neurosci 9, 445.

Wechsler, D., 1997. Wechsler memory scale (WMS-III). Psychological Corporation.

Woicik, P.A., Moeller, S.J., Alia-Klein, N., Maloney, T., Lukasik, T.M., Yeliosof, O., Wang, G.J., Volkow, N.D., Goldstein, R.Z., 2009. The neuropsychology of cocaine addiction: recent cocaine use masks impairment. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 34, 1112-1122.

Wunderli, M.D., Vonmoos, M., Niedecker, S.M., Hulka, L.M., Preller, K.H., Baumgartner, M.R., Kraemer, T., Seifritz, E., Schaub, M.P., Eich-Hochli, D., Quednow, B.B., 2016. Cognitive and emotional impairments in adults with attention-deficit/hyperactivity disorder and cocaine use. Drug Alcohol Depend 163, 92-99.

Table 1: Hair analyses parameters for all groups.

	Controls (n=56)	Primary MDMA (n=26)	Polydrug MDMA (n=25)
MDMA			
Hair analysis pg/mgd	0.00 (0.00)	3414 (9184)	4894 (5398)
Min / max hair value	0.00 / 0.00	32 / 48000	134 / 17500
N > 0	0	26	25
MDEA			
Hair analysis pg/mgd	0.00 (0.00)	7.5 (23.64)	12.96 (31.54)
Min / max hair value	0.00 / 0.00	0 / 114	0 / 145
N > 0	0	4	6
MDA			
Hair analysis pg/mgd	0.00 (0.00)	90.15 (79.68)	187.96 (247.2)
Min / max hair value	0.00 / 0.00	0 / 331	0 / 1088
N > 0	0	25	23
Amphetamine			
Hair analysis pg/mg	0.00 (0.00)	38.5 (63.8)	801.0 (1804)
Min / max hair valuen	0.00 / 0.00	0 / 195	0 / 8324
N > 0	0	9	17
Methamphetamine			
Hair analysis pg/mgd	0.00 (0.00)	0.00 (0.00)	42.2 (152.04)
Min / max hair value	0.00 / 0.00	0.00 / 0.00	0 / 730
N > 0	0	0	3
Cocaine			
Hair analysis pg/mg	0.00 (0.00)	63.8 (111.5)	3893 (5554)
Min / max hair value	0.00 / 0.00	0 / 445	73 / 24500
N > 0	0	10	25
MPH			
Hair analysis pg/mgd	0.00 (0.00)	0.00 (0.00)	3.98 (17.93)
Min / max hair value	0.00 / 0.00	0 / 0	0 / 98.5
N > 0	0	0	2
Morphine			
Hair analysis pg/mgd	0.00 (0.00)	0.00 (0.00)	8 (40)
Min / max hair value	0.00 / 0.00	0 / 0	0 / 200
N > 0	0	0	1
Codeine			
Hair analysis pg/mgd	0.00 (0.00), n=32	0.00 (0.00), n=3	106.11 (307.24), n=9
Min / max hair value	0.00 / 0.00	0 / 0	0 / 925
N > 0	0	0	2
Methadone			
Hair analysis pg/mgd	0.00 (0.00)	0.00 (0.00)	2.4 (12)
Min / max hair value	0.00 / 0.00	0 / 0	0 / 60
N > 0	0	0	1
2C-B			
Hair analysis pg/mgd	0.00 (0.00), n=10	4.4 (15.4), n=25	11 (24.56), n=11
Min / max hair value	0.00 / 0.00	0 / 63	0 / 65
N > 0	0	2	2
Ketamine			
Hair analysis pg/mgd	0.00 (0.00), n=10	13.26 (52.86), n=23	89.8 (127.52), n=10
Min / max hair value	0.00 / 0.00	0 / 250	0 / 380
N > 0	0	2	5

Means, standard deviations, minimum and maximum for metabolites (pg/mg) are shown. If hair analyses were not available for some participants, sample size n for participants with hair analyses is shown. The cocaine metabolites benzoylecgonine, cocaethylene, and norcocaine are not shown. Tramadol and 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP) are not shown because they were not detected.

EDDP, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene; MDA, 3,4-Methylendioxyamphetamine; MDEA, 3,4-Methylendioxy-N-ethylamphetmanine; MDMA, 3,4-Methylendioxy-N-methylamphetmanine; 2C-B, 2,5-dimethoxy-4-bromphenethylamine.

Table 2: Demographic data and drug use (means and standard deviations)

	Controls	Primary MDMA	Polydrug MDMA	*value*	*p*	df
n	56	26	25			
Age, years	25.8 (6.1)	26.6 (7.0)	26.7 (5.8)	0.25	0.78	2
Years of school education	11.02 (1.6)	10.5 (1.8)	10.2 (1.9)	2.14	0.12	2
Verbal intelligence	103.9 (8.2)	102.8 (8.3)	100.9 (8.3)	1.15	0.32	2
Beck's Depression Inventory score	3.5 (3.8)	4.4 (4.8)	5.2 (4.9)	1.29	0.28	2
ADHD-SR score	7.7 (5.1)	12.8 (8.5)**	11.76 (7.7)*	6.57	**0.00**	2
ADHD (y/n)[a]	0/56	3/23	4/21	8.64	**.01**	2
Sex (female/male)	26/30	15/11	9/16	2.41	0.30	2
Tobacco						
Smoking status (y/n)[b]	41/15	18/8	24/1*[#]	6.53	**0.04**	2
Cigarettes per day[b]	7.3 (10.1)	5.6 (8.2)	11.8 (7.6)*[#]	3.30	**0.04**	2
Years of use	6.0 (6.6)	4.5 (6.1)	8.8 (5.6)[#]	3.05	0.05	2
Alcohol						
Grams per week[b]	117.9 (132.0)	138.1 (119.6)	184.3 (126.5)*	2.33	0.10	2
Years of use	8.7 (6.5)	6.6 (7.1)	8.1 (5.7)	0.99	0.37	2
Cannabis						
Status (y/n)[b]	30/26	19/7	15/10	2.81	0.25	2
Grams per week[b]	0.44 (1.04)	0.60 (1.3)	0.67 (1.4)	0.35	0.70	2
Years of use	3.3 (3.7)	4.4 (5.1)	4.5 (4.5)	0.90	0.41	2
Cumulative dose (grams)	195.7 (504.6)	543.1 (962.8)	767.4 (1153)*	4.69	**0.01**	2
Positive urine testing (n/y)[c,d]	48/7	21/5	21/4	0.60	0.74	2
Last consumption (days)	23.1 (32.9) n=30	18.0 (36.1) n=19	12.7 (23.3) n=15	0.55	0.58	2
Last consumption (range, days)[e]	3 / 111	3 / 152	3 / 91			
MDMA						
Tablets per week[b,f]	0.00 (0.00)	0.91 (0.89)***	0.8 (1.1)***	23.07	**0.00**	2
Years of use	0.00 (0.00)	3.4 (3.2)***	3.6 (2.5)***	41.64	**0.00**	
Cumulative dose (grams)	0.13 (0.04)	26.6 (32.3)***	21.0 (30.2)***	17.66	**0.00**	2
Last consumption (days)	-	25.9 (21.4) n=26	43.0 (79.1) n=20	1.12	0.30	1
Last consumption (range, days)[e]	-	4 / 98	4 / 365			
Amphetamine						
Status (y/n)[b]	0/56	12/14***	18/7***	50.00	**0.00**	2
Dependence (y/n)[a]	0/56	26/0	23/2	6.69	**0.04**	2
Grams per week[b]	0.00 (0.00)	0.01 (0.02)	0.11 (0.14)***[###]	22.93	**0.00**	2
Years of use	0.00 (0.00)	1.9 (3.3)***	2.2 (2.9)***	12.34	**0.00**	2
Last consumption (days)	-	34.1 (44.3) n=12	27.6 (25.2) n=18	0.26	0.61	1
Last consumption (range, days)[e]	-	3 / 122	5 / 91			
Cumulative dose (grams)	0.01 (0.03)	35.0 (129.6)*	26.0 (57.9)	2.79	0.07	2
Positive urine testing (n/y)[c,d]	55/0	26/0	24/1	3.27	0.20	2
Cocaine						
Status (y/n)[b]	0/56	10/16***	22/3***[###]	65.05	**0.00**	2
Dependence (y/n)[a]	56/0	26/0	23/2	6.69	**0.04**	2
Grams per week[b]	0.00 (0.00)	0.03 (0.08)	0.62 (0.72)***[###]	29.35	**0.00**	2
Years of use	0.00 (0.00)	1.4 (3.1)*	4.9 (4.3)***[###]	32.36	**0.00**	2
Last consumption (days)	-	33.8 (40.9) n=10, 9/57	19.2 (23.5) n=22, 5/22	1.65	0.21	1
Last consumption (range, days)[e]	-	4 / 122	3 / 91			

Cumulative dose (grams)	0.02 (0.05)	41.1 (162.3)	198.4 (259.1)***###	15.60	**0.00**	2
Positive urine testing (n/y)[c,d]	55/0	26/0	22/3*	10.00	**0.01**	2
Ketamin						
Status (y/n)[b]	0/56	2/24	6/19***	14.40	**0.00**	2
Last consumption (days)	-	60.0 (17.0) n=2	244 (257.8) n=6	-	-	-
Last consumption (range, days)[e]	-	14 / 21	5 / 196			
Cumulative occasions	0.00 (0.00)	1.31 (3.98)	2.86 (5.17)	7.26	**0.00**	2

Significant *p*-values ($p<.05$) are shown in bold. Statistical tests: ANOVA (all groups), $\chi 2$ test (all groups) for frequency data or independent t test (two groups).
ADHD, attention-deficit/hyperactivity disorder;
Consumption per week, duration of use, and cumulative dose are averages within the total group.
Last consumption is an average only for persons who reported to have used the drug within the past 6 months. In this case, sample size (n) is shown.
[a]According to DSM-IV criteria.
[b]During the past 6 months.
[c]For cut-offs, see the Supplementary Methods S2.
[d]One urine sample (control) was missing.
[e]min / max
[f]In 100-mg tablets.
Post-hoc tests vs. controls: *$p<.05$, ** $p<.01$, ***$p<.001$; vs. primary MDMA $^{\#}p<.05$, $^{\#\#}p<.01$, $^{\#\#\#}p<.001$.

Table 3: Cognitive parameters and domain scores.

				Controls vs. primary MDMA	Controls vs. polydrug MDMA	Primary vs. polydrug MDMA
Cognitive parameters and domain scores	**Controls**	**Primary MDMA users**	**Polydrug MDMA users**	***p***	***p***	***p***
n	56	26	25			
Attention	0.00 (0.78)	-0.19 (0.86)	-0.61 (0.95)	.350	**.003**	.074
RAVLT Supraspan trial 1	9.6 (2.6)	8.8 (2.0)	7.9 (2.4)	.182	**.003**	.152
RVP Discrimination performance A'	0.92 (0.04)	0.92 (0.05)	0.90 (0.05)	.575	**.023**	.135
RVP Total hits	18.8 (4.3)	18.3 (5.0)	16.4 (5.1)	.652	**.040**	.162
Working memory	0.00 (0.60)	-0.36 (0.79)	-0.7 (0.9)	**.034**	**.000**	.064
LNST Score	15.9 (3.1)	15.2 (2.8)	13.8 (2.1)	.356	**.008**	.126
SWM Total errors[a]	15.6 (12.2)	17.9 (15.7)	22.8 (16.4)	.498	**.040**	.222
PAL First trial memory score	16.9 (2.6)	15.1 (3.4)	14.2 (3.1)	**.011**	**.000**	.248
Memory	0.00 (0.76)	-0.77 (0.81)	-1.7 (1.8)	**.004**	**.000**	**.003**
RAVLT Learning performance	64.8 (6.0)	60.8 (5.4)	56.4 (8.3)	**.011**	**.000**	**.040**
RAVLT Delayed recall	14.0 (1.5)	12.7 (1.6)	11.4 (2.5)	**.004**	**.000**	**.029**
RAVLT Recognition performance adj.	0.91 (0.08)	0.86 (0.07)	0.8 (0.2)	**.038**	**.001**	.202
PAL Total trials adj.	7.2 (1.5)	8.3 (2.2)	10.1 (3.7)	**.046**	**.000**	**.014**
PAL Total errors adj.	5.6 (4.3)	9.5 (7.0)	17.8 (19.0)	.106	**.000**	**.008**
Executive functions	0.00 (0.66)	-0.36 (0.96)	-0.81 (1.2)	.093	**.000**	.073
RAVLT Recall consistency (%)	94.7 (4.6)	90.6 (5.4)	86.6 (8.9)	**.005**	**.000**	**.033**
SWM Strategy score[a]	31.7 (5.4)	30.5 (6.1)	33.7 (4.1)	.378	.127	**.041**
IED Total trials adj.	97.2 (49.9)	36.7 (44.6)	44.1 (54.9)	.243	.060	.525
IED Total errors adj.	26.3 (28.7)	116.4 (76.4)	131.0 (95.3)	.273	.086	.581

Significant *p*-values ($p<.05$) are shown in bold. Statistical tests: Multiple linear regression with the dummy coded factors controls vs. primary MDMA users and controls vs. polydrug MDMA users (t-test) or polydrug MDMA users vs. controls and polydrug MDMA users vs. primary MDMA users.

IED, Intra-Extra Dimensional Set Shift Task; LNST, Letter Number Sequencing Task; PAL, Paired Associates Learning; RAVLT, Rey Auditory Verbal Learning Test; RVP, Rapid Visual Information Processing; SWM, Spatial Working Memory.

[a] Data of one participant (polydrug MDMA) are missing due to a technical failure.

Figure Captions

Figure 1: Cohen's *d* effect sizes for primary and polydrug MDMA users vs. controls over the cognitive domains.

Significant dummy coded group contrasts of controls (n=56) vs. primary MDMA users (n=26): **p*<.05, ***p*<.01; vs. polydrug MDMA users (n=25): $^{\#\#}p$<.01, $^{\#\#\#}p$<.001 are shown.

Figure 2: Cohen's *d* effect sizes for primary and polydrug MDMA users vs. controls over single parameters.

Significant dummy coded group contrasts of controls (n=56) vs. primary MDMA users (n=26): **p*<.05, ***p*<.01; vs. polydrug MDMA users (n=25): $^{\#}p$<.05, $^{\#\#}p$<.01, $^{\#\#\#}p$<.001 are shown.
IED, Intra-Extra Dimensional Set Shift Task; LNST, Letter Number Sequencing Task; PAL, Paired Associates Learning; RAVLT, Rey Auditory Verbal Learning Test; RVP, Rapid Visual Information Processing; SWM, Spatial Working Memory.

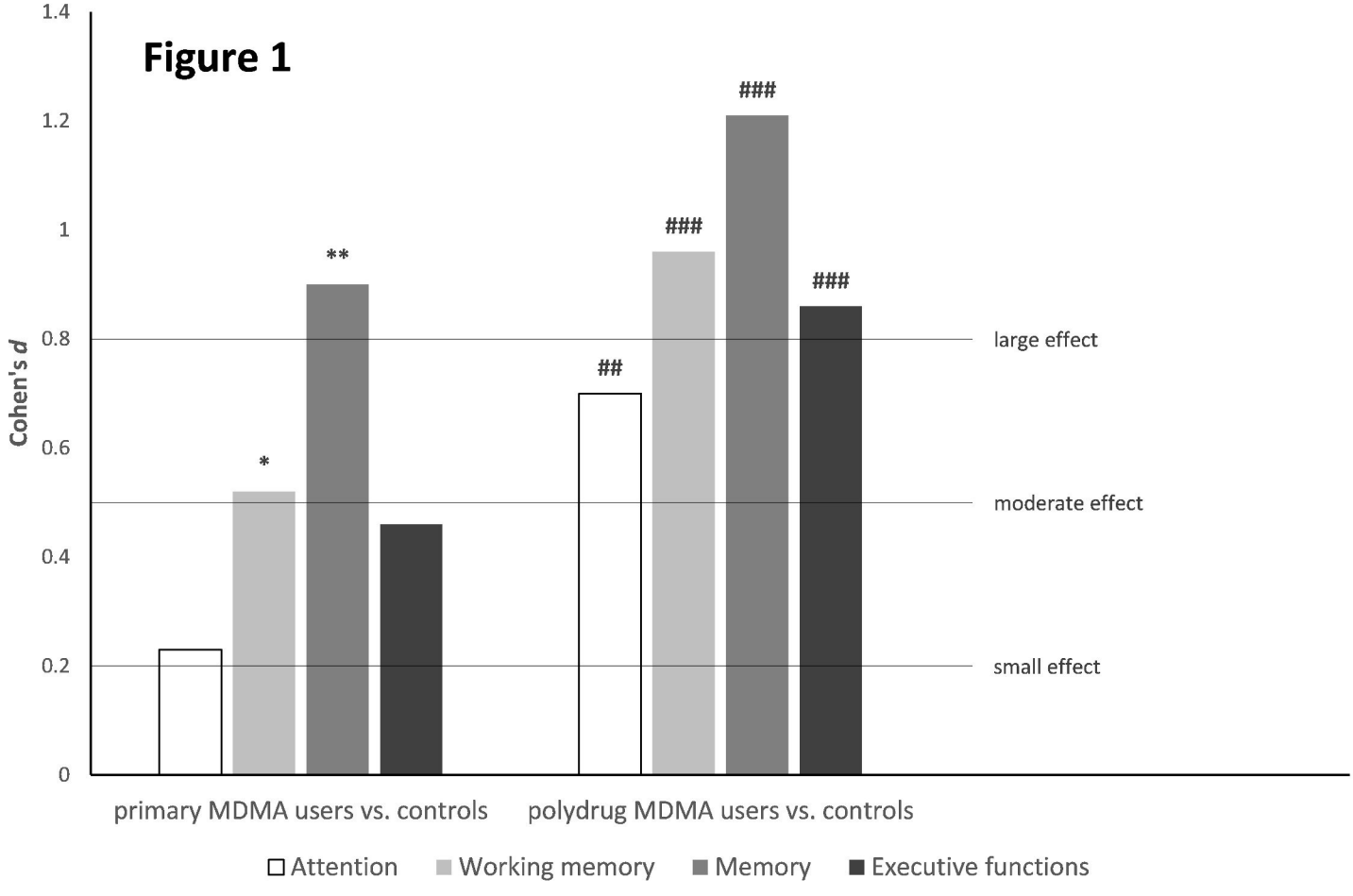
Figure 1
Cohen's d
1.4
1.2
1
0.8
0.6
0.4
0.2
0
large effect
moderate effect
small effect
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primary MDMA users vs. controls
polydrug MDMA users vs. controls
Attention
Working memory
Memory
Executive functions

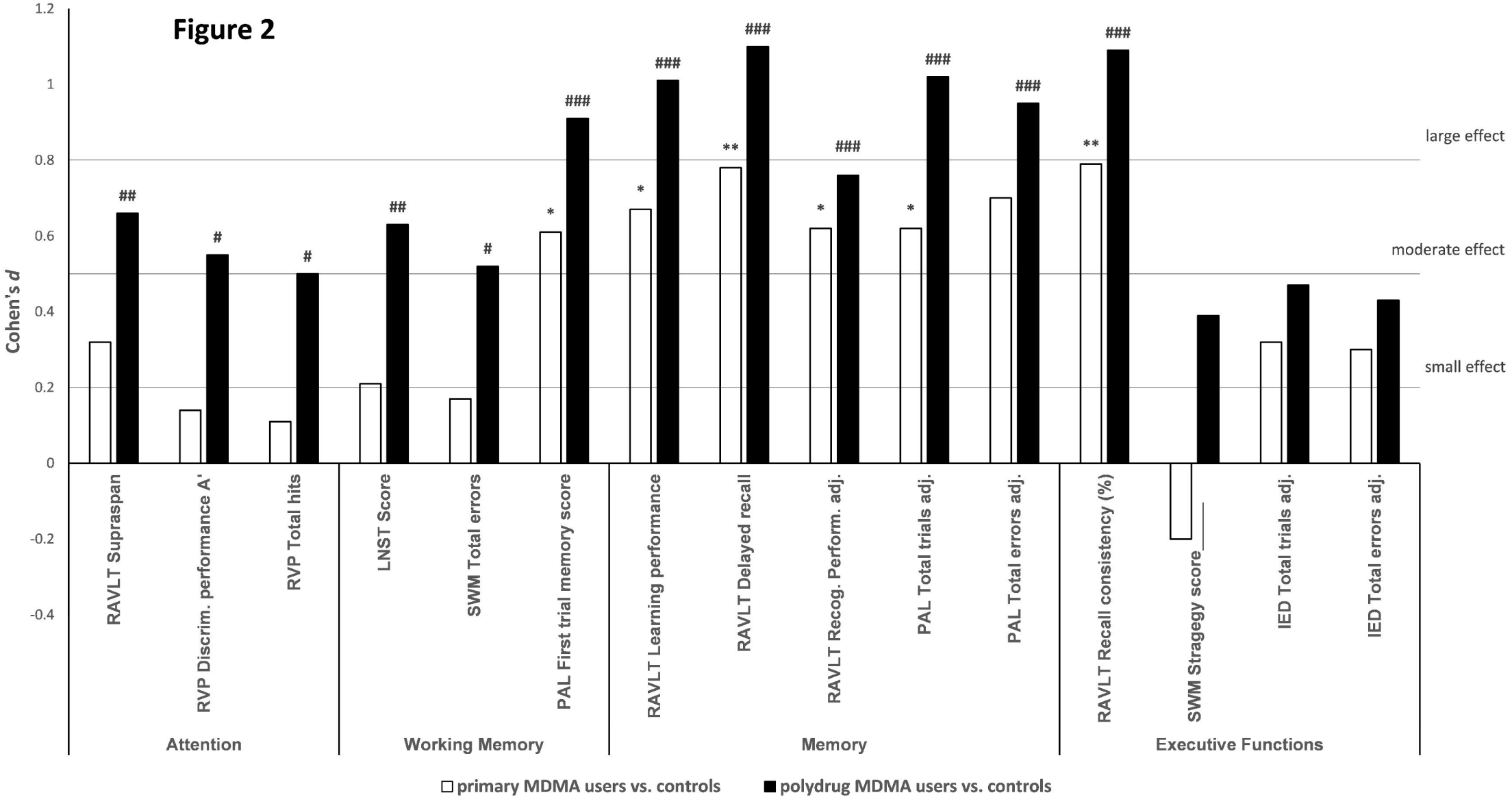
Figure 2
Cohen's d
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
large effect
moderate effect
small effect
RAVLT Supraspan
RVP Discrim. performance A'
RVP Total hits
LNST Score
SWM Total errors
PAL First trial memory score
RAVLT Learning performance
RAVLT Delayed recall
RAVLT Recog. Perform. adj.
PAL Total trials adj.
PAL Total errors adj.
RAVLT Recall consistency (%)
SWM Stragegy score
IED Total trials adj.
IED Total errors adj.
Attention
Working Memory
Memory
Executive Functions
primary MDMA users vs. controls
polydrug MDMA users vs. controls

Data Supplement

Article Title: Discrete memory impairments in largely pure long-term users of MDMA

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Methods S1: Urine and hair toxicology

Urine toxicology analyses comprised the following substances: tetrahydrocannabinol, cocaine, amphetamines, benzodiazepines, opioids, and methadone and were assessed by a semi-quantitative enzyme multiplied immunoassay method using a Dimension RXL Max (Siemens, Erlangen, Germany). For the detection of illegal drug use, the following cut-offs have been applied (Bush, 2008): Cannabis, 50 ng/ml; cocaine, 150 ng/ml; and amphetamines, 500 ng/ml.

To objectively characterize drug use over the last six months, hair samples were collected and analyzed with liquid chromatography-tandem mass spectrometry (LC-MS/MS). The proximal hair segment of a length of up to 6 cm was examined. The following 17 compounds were assessed: cocaine, benzoylecgonine, cocaethylene, norcocaine, amphetamine, methamphetamine, MDMA, MDEA, MDA, morphine, codeine, methadone, EDDP (primary methadone metabolite, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene), tramadol, 2C-B, ketamine, and methylphenidate.

For our routine protocol for drugs of abuse analysis a three-step washing procedure with water (2 minutes shaking, 15ml), acetone (2min., 10ml) and finally hexane (2min., 10ml) of hair was performed. Then the hair samples were dried at ambient temperatures, cut into small snippets and extracted in two steps, first with methanol (5ml, 16 hours, ultrasonication) and a second step with 3 ml MeOH acidified with 50 µL hydrochloric acid 33 % (3 hours, ultrasonication). The extracts were dried and the residue reconstituted with 50 µL MeOH and 500 µL 0.2 mM ammonium formate (analytical grade) in water. As internal standards deuterated standards of the following compounds were used, added as mixture of the following compounds: cocaine-d3, benzoylecgonine-d3, ethylcocaine-d3, morphine-d3, MAM-d3, codeine-d3, dihydrocodeine-d3, amphetamine-d6, methamphetamine-d9, MDMA-d5. MDEA-d6, MDA-d5, methadone-d9, EDDP-d3, methylphenidate-d9, tramadol-d3, oxycodone-d3, and ephedrine-d3. All deuterated standards were from ReseaChem (Burgdorf, Switzerland), the solvents for washing and extraction were of analysis grade and obtained from Merck (Darmstadt, Germany); LC-solvents were of HPLC grade and were obtained from Sigma Aldrich (Buchs, Switzerland).

The LC-MS/MS apparatus was an ABSciex QTrap 3200 (Analyst software Version 1.5, Turbo V ion source operated in the ESI mode, gas 1, nitrogen (50 psi); gas 2, nitrogen (60 psi); ion spray voltage, 3500V; ion source temperature, 450°C; curtain gas, nitrogen (20 psi) collision gas, medium), with a Shimadzu Prominence LC-system (Shimadzu CBM 20 A controller, two Shimadzu LC 20 AD pumps including a degasser, a Shimadzu SIL 20 AC autosampler and a Shimadzu CTO 20 AC column oven, Shimadzu, Duisburg, Germany). Gradient elution was performed on a separation column (Synergi 4µ POLAR-RP 80A, 150x2.0 with a POLAR-RP 4x2.0 Security Guard Cartridge, (Phenomenex, Aschaffenburg, Germany). The mobile phase consisted of 1mM ammonium formate buffer adjusted to pH 3,5 with formic acid (eluent A) and acetonitrile containing 1mM ammonium formate and 1 mM formic acid (eluent B). The analysis was performed in MRM mode with two transitions per analyte and one transition for each deuterated internal standard, respectively. According to the Society of Hair Testing (Society of Hair, 2004), the following cut-offs have been applied: cocaine, 500 pg/mg; amphetamine, 200 pg/mg; and MDMA, 200 pg/mg.

Methods S2: Construction of cognitive domain scores

Fifteen predefined main cognitive test parameters were z-transformed on the basis of means and standard deviations of the control group as published before (Vonmoos et al., 2013). If necessary, test scores were reversed so that high scores always indicated a better cognitive performance. These parameters were reduced to the four cognitive domains attention, working memory, declarative memory, and executive function. Furthermore, these four z-scored domains were equally integrated into a broad global cognitive index (GCI).

Attention: To assess attentional capacity, we focused primarily on sustained attention by including the two Rapid Visual Information Processing (RVP) parameters discrimination performance A' and total of hits

(Jones et al., 1992). In order to diversify this domain we added the Ray Auditory Verbal Learning Test (RAVLT) parameter trial 1, a supraspan measure with a large attentional component (Lezak et al., 2004).

Working Memory: The Spatial Working Memory (SWM) parameter number of total errors tested the capability to retain spatial information and to manipulate remembered items in working memory (Morris et al., 1988). The Letter Number Sequencing Test (LNST) measured the verbal working memory by summing up the number of correct responses (Wechsler, 1997). The third parameter was the number of correctly located patterns after the first presentation, a Paired Associates Learning (PAL) parameter measuring primarily a visual working memory component (Sahakian et al., 1988).

Declarative memory: The RAVLT was administered to assess the verbal declarative memory performance (Helmstaedter et al., 2001). Performance was measured by the parameters learning performance (∑trials 1-5), delayed recall (trial 7), and an adjusted recognition performance (p(A)) (Helmstaedter et al., 2001). To capture the visual declarative memory, we used the two PAL parameters: adjusted total of errors and adjusted total of trials (Sahakian et al., 1988).

Executive Functions: The Intra/Extra-Dimensional Set Shifting Task (IED) assessed visual discrimination, attentional set formation, maintenance, shifting, and flexibility (Downes et al., 1989). The considered test parameters were the total of errors and trials adjusted to the amount of completed stages. Hereby, we added the SWM strategy score assessing the applied heuristic strategies (Morris et al., 1988), and the RAVLT recall consistency, a parameter impaired in patients with prefrontal lesions (Alexander et al., 2003; Benedict et al., 2005; Jokeit et al., 1997) and related with measures of executive functions (Beebe et al., 2000).

Table S1: Hair analyses results (concentration values in pg/mg) and MDMA group allocation.

Subject	Hair sample taken?	MDMA group	MDMA	MDEA	MDA	Amphet-amine	Methamphet-amine	Cocaine	Methyl-phenidate	Morphine/ Codeine	Methadone/ EDDP	2C-B	Ketamine	Hair length[1]
1	yes	primary	1985	0	55	0	0	445	0	0	0	0	n.a.	6
2	yes	primary	975	0	30	55	0	45	0	0	0	n.a.	n.a.	6
3	yes	primary	48000	40	150	60	0	80	0	0	0	0	n.a.	3.5
4	yes	primary	1673	0	102	0	0	0	0	0	0	47	0	6
5	yes	primary	915	0	45	59	0	156	0	0	0	0	0	2
6	yes	primary	780	21	50	0	0	169	0	0	0	0	0	6
7	yes	primary	4813	0	244	25	0	0	0	0	0	0	0	6
8	yes	primary	2239	0	121	0	0	0	0	0	0	0	0	3.5
9	yes	primary	2982	0	165	0	0	298	0	0	0	63	0	6
10	yes	primary	1440	0	60	122	0	0	0	0	0	0	0	3.5
11	yes	primary	626	0	41	0	0	0	0	0	0	0	0	6
12	yes	primary	2408	114	117	160	0	0	0	0	0	0	0	6
13	yes	primary	1763	0	125	15	0	0	0	0	0	0	0	6
14	yes	primary	1054	0	60	191	0	78	0	0	0	0	250	6
15	yes	primary	231	0	6	0	0	0	0	0	0	0	0	6
16	yes	primary	1369	0	67	0	0	0	0	0	0	0	0	4
17	yes	primary	2510	20	79	0	0	0	0	0	0	0	0	6
18	yes	primary	534	0	9	0	0	0	0	0	0	0	0	6
19	yes	primary	4670	0	331	0	0	81	0	0	0	0	0	6
20	yes	primary	2695	0	182	0	0	0	0	0	0	0	0	6
21	yes	primary	471	0	29	0	0	87	0	0	0	0	0	6
22	yes	primary	2232	0	55	0	0	0	0	0	0	0	55	6
23	yes	primary	32	0	5	0	0	0	0	0	0	0	0	6
24	yes	primary	2625	0	119	195	0	0	0	0	0	0	0	6
25	yes	primary	118	0	0	0	0	0	0	0	0	0	0	6
26	yes	primary	123	0	9	0	0	219	0	0	0	0	0	6
27	yes	poly	17500	0	750	180	0	**7700**	0	0	0	n.a.	n.a.	6

28	yes	poly	10659	43	266	**755**	0	73	0	0	0	0	191	1.5
29	yes	poly	14863	31	317	0	0	**2515**	0	0	0	0	174	5
30	yes	poly	2298	54	117	93	0	**713**	0	0	0	0	0	6
31	yes	poly	754	0	50	0	0	**7233**	0	0	0	0	0	1.5
32	yes	poly	12639	22	144	0	0	**803**	0	0	0	0	0	6
33	yes	poly	6050	0	303	**8324**	245	**4243**	0	0	0	0	31	6
34	yes	poly	15731	29	1088	**4228**	0	**1178**	0	0	0	65	0	6
35	yes	poly	1778	0	116	**540**	0	**1583**	0	0	0	0	122	6
36	yes	poly	134	0	0	**808**	0	88	0	0	0	56	0	6
37	yes	poly	146	0	0	**1013**	0	216	0	0	0	0	380	6
38	yes	poly	4650	0	195	**730**	0	**24500**	0	30	0	n.a.	n.a.	6
39	yes	poly	2000	0	30	140	0	**1000**	0	0	0	n.a.	n.a.	1.5
40	yes	poly	1200	0	20	0	0	**2000**	0	0	0	n.a.	n.a.	3
41	yes	poly	1150	0	100	**325**	0	**1275**	0	0	0	n.a.	n.a.	6
42	yes	poly	850	0	50	0	0	**2800**	0	0	0	n.a.	n.a.	6
43	yes	poly	3150	0	215	105	730	**590**	0	0	0	n.a.	n.a.	6
44	yes	poly	835	0	15	0	0	**2900**	0	925	0	n.a.	n.a.	6
45	yes	poly	6350	0	307.5	0	80	**1750**	0	0	0	n.a.	n.a.	6
46	yes	poly	1000	0	35	0	0	**3300**	0	200	60	n.a.	n.a.	1.5
47	yes	poly	3750	145	150	**1850**	0	**15000**	0	0	0	n.a.	n.a.	6
48	yes	poly	10000	0	250	**440**	0	**10000**	0	0	0	n.a.	n.a.	1.5
49	yes	poly	2050	0	65	**230**	0	**3450**	0	0	0	n.a.	n.a.	6
50	yes	poly	570	0	48	**210**	0	480	10	0	0	n.a.	n.a.	2.5
51	yes	poly	2265	0	67.5	55	0	**1950**	89.5	0	0	n.a.	n.a.	4
52	no	none	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0	n.a.	n.a.	-
53	no	none	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0	n.a.	n.a.	-

For each participant, the amount of metabolites per substance (pg/mg) and the group are shown. The cocaine metabolites benzoylecgonine, cocaethylene, and norcocaine are not shown. Tramadol is not shown because it was not detected. Reasons for polydrug MDMA classification are shown in bold.
To be included into the primary MDMA group, hair samples had to reveal a cocaine value <500pg/mg and an amphetamine value <200pg/mg (Cooper et al., 2012).
[1] analyzed hair length from scalp in cm.
EDDP, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene; MDA, 3,4-Methylendioxyamphetamine; MDEA, 3,4-Methylendioxy-N-ethylamphetmanine; MDMA, 3,4-Methylendioxy-N-methylamphetmanine; n.a., not available; 2C-B, 2,5-dimethoxy-4-bromphenethylamine.

Table S2: Multiple Regression analysis for demographic variables, group contrasts and psychopathology predicting memory performance.

	B	SE *B*	β
Step 2			
Constant	-.191	.229	
primary MDMA vs. Controls	-.828	.271	-.270**
poly MDMA vs. Controls	-1.603	.268	-.523***
Sex	-.041	.214	-.016
Age	-.041	.018	-.194*
Verbal IQ	.037	.013	.232**
BDI sum score	-.045	.027	-.150
ADHD sum score	.028	.018	.148

Dependent variable: declarative memory performance (z-score).
N = 106 (26 primary MDMA users, 25 poly MDMA users, and 56 controls).
R^2 = .37 and F = 11.753 (p<.001) for Step 1, ΔR^2 = .021 and ΔF = 1.726 (p = .183) for Step 2.
The data met the assumption of independent errors (Durbin-Watson value = 2.13).
ADHD = Attention Deficit / Hyperactivity Disorder, ADHD sum score = Sum of Items 1 to 18, *B* = regression coefficient, β = standardized Beta, BDI = Beck's Depression Inventory, SE *B* = standard error.
Age is centered at the overall mean age (26.21 years) and verbal IQ is centered at 100 IQ points. Females were coded with 1 and males with 0 for the sex variable.
* *p* <.05, ** *p* <.01, *** *p* <.001

Table S3: Multiple Regression analysis for drug use variables covering consumption over the past half year predicting memory performance.

	B	*SE B*	*β*
Constant	11.415	6.388	
primary MDMA vs. poly MDMA	-.810	.419	-.279(*)
Cannabis (g/week)	-.232	.152	-.208
Nicotine (cigarettes per day)	-.039	.026	-.224
Alcohol (g/week)	.001	.002	.108
MDMA hair concentration (pg/mg)	.000	.000	.213

Dependent variable: declarative memory performance (z-score).
N = 51 (26 primary MDMA users, 25 poly MDMA users).
R^2 = .21 and F = 2.372 (p=.054).
The data met the assumption of independent errors (Durbin-Watson value = 2.55).
B = regression coefficient, β = standardized Beta, g/week = grams per week, pg/mg = picogram per milligram, SE *B* = standard error.
Poly MDMA users were coded with 1 and primary MDMA users with 0 for the group comparison.
(*) *p* =.059,

Table S4: Multiple Regression analysis for drug use variables covering consumption over the lifetime predicting memory performance.

	B	*SE B*	*β*
Constant	11.232	6.498	
primary MDMA vs. poly MDMA	-.773	.423	-.266(*)
Alcohol (years of use)	-.018	.035	-.080
Nicotine (years of use)	-.016	.039	-.067
Cannabis lifetime dose (g)	-.000	.000	-.271*
MDMA lifetime dose (tablets[1])	-.000	.001	-.011

Dependent variable: declarative memory performance (z-score).
N = 51 (26 primary MDMA users, 25 poly MDMA users).
R^2 = .19 and F = 2.103 (p=.083).
The data met the assumption of independent errors (Durbin-Watson value = 2.40).
B = regression coefficient, β = standardized Beta, g = grams, SE *B* = standard error.
[1] tablets à 100mg
Poly MDMA users were coded with 1 and primary MDMA users with 0 for the group comparison.
(*) *p* =.075, **p*=.052

References

Alexander, M.P., Stuss, D.T., Fansabedian, N., 2003. California Verbal Learning Test: performance by patients with focal frontal and non-frontal lesions. Brain 126, 1493-1503.

Beebe, D.W., Ris, M.D., Dietrich, K.N., 2000. The relationship between CVLT-C process scores and measures of executive functioning: lack of support among community-dwelling adolescents. J. Clin. Exp. Neuropsychol. 22, 779-792.

Benedict, R.H., Zivadinov, R., Carone, D.A., Weinstock-Guttman, B., Gaines, J., Maggiore, C., Sharma, J., Tomassi, M.A., Bakshi, R., 2005. Regional lobar atrophy predicts memory impairment in multiple sclerosis. AJNR Am. J. Neuroradiol. 26, 1824-1831.

Bush, D.M., 2008. The U.S. Mandatory Guidelines for Federal Workplace Drug Testing Programs: current status and future considerations. Forensic Sci. Int. 174, 111-119.

Cooper, G.A., Kronstrand, R., Kintz, P., Society of Hair, T., 2012. Society of Hair Testing guidelines for drug testing in hair. Forensic Sci Int 218, 20-24.

Downes, J.J., Roberts, A.C., Sahakian, B.J., Evenden, J.L., Morris, R.G., Robbins, T.W., 1989. Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease: evidence for a specific attentional dysfunction. Neuropsychologia 27, 1329-1343.

Helmstaedter, C., Lendt, M., Lux, S., 2001. Verbaler Lern- und Merkfähigkeitstest. Beltz, Göttingen.

Jokeit, H., Seitz, R.J., Markowitsch, H.J., Neumann, N., Witte, O.W., Ebner, A., 1997. Prefrontal asymmetric interictal glucose hypometabolism and cognitive impairment in patients with temporal lobe epilepsy. Brain 120, 2283-2294.

Jones, G.M., Sahakian, B.J., Levy, R., Warburton, D.M., Gray, J.A., 1992. Effects of acute subcutaneous nicotine on attention, information processing and short-term memory in Alzheimer's disease. Psychopharmacology (Berl.) 108, 485-494.

Lezak, M., Howieson, D., Loring, D., Hannay, H., Fischer, J., 2004. Neuropsychological assessment (4th ed.) Oxford University Press, New York.

Morris, R.G., Downes, J.J., Sahakian, B.J., Evenden, J.L., Heald, A., Robbins, T.W., 1988. Planning and spatial working memory in Parkinson's disease. J. Neurol. Neurosurg. Psychiatry 51, 757-766.

Preller, K.H., Hulka, L.M., Vonmoos, M., Jenni, D., Baumgartner, M.R., Seifritz, E., Dziobek, I., Quednow, B.B., 2014. Impaired emotional empathy and related social network deficits in cocaine users. Addiction biology 19, 452-466.

Sahakian, B.J., Morris, R.G., Evenden, J.L., Heald, A., Levy, R., Philpot, M., Robbins, T.W., 1988. A comparative study of visuospatial memory and learning in Alzheimer-type dementia and Parkinson's disease. Brain 111, 695-718.

Society of Hair, T., 2004. Recommendations for hair testing in forensic cases. Forensic Sci. Int. 145, 83-84.

Vonmoos, M., Hulka, L.M., Preller, K.H., Jenni, D., Baumgartner, M.R., Stohler, R., Bolla, K.I., Quednow, B.B., 2013. Cognitive dysfunctions in recreational and dependent cocaine users: role of attention-deficit hyperactivity disorder, craving and early age at onset. The British journal of psychiatry : the journal of mental science 203, 35-43.

Vonmoos, M., Hulka, L.M., Preller, K.H., Minder, F., Baumgartner, M.R., Quednow, B.B., 2014. Cognitive impairment in cocaine users is drug-induced but partially reversible: evidence from a longitudinal study. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 39, 2200-2210.

Wechsler, D.A., 1997. Wechsler Memory Scale (3rd ed.). Manual. Psychological Corporation, San Antonio, TX.